第 23 回日本がん免疫学会総会

一般演題（ポスター） 腫瘍抗原・ネオアンチゲンの探索
8 月 22 日 17 : 50~18 : 50 ポスター会場 II
P04-5 lmmunogenicity of frequent driver mutations; identification of novel HLA class II-restricted neoantigens

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Many clinical trials of cancer vaccines have been performed, with limited success so far. Such unexpected results could be explained, at least in part, by inappropriate selection of vaccine antigens employed, be− cause most of them are derived from non-mutated self-antigens, which cannot be expected to show high immunogenicity because of the tolerance mechanism. Recently, increasing attention has been paid to neoantigens derived from somatic genetic mutations that are specifically present in cancer cells, because they can be recognized as non-self by the immune system and are expected to induce stronger immune re−sponses. In particular, since "driver mutations" that are directly involved in malignant processes are frequently shared by patients with various types of cancers and do not disappear easily by immune escape, they could represent appropriate off-the-shelf targets for cancer immunotherapy. However, limited information is available regarding the immunogenicity of driver mutations.
In the current study, we evaluated the immunogenicity of 10 driver mutations (KRAS-Gl2D, -Gl2V, -Gl2 C, -Gl2R, -Gl3D: NRAS-Q61K, -Q61R: PIK3CA-E545K, -Hl047R: and C-Kit-D816V) that are frequently expressed in various cancers. A panel of long synthetic peptides (27mer) derived from these mutations were examined for HLA class I- and class II-restricted T cell responses, by using PBMC from healthy donors (n = 25), and the following results were obtained.
1. Of the 10 synthetic peptides, six peptides from KRAS-Gl2D, KRAS-Gl2R. KRAS-Gl3D, NRAS-Q61R, PIK3CA-Hl047R, and C-Kit-D816V induced T cell responses.
2. All six peptides induced HLA class II-restricted $CD4^+$ T cell responses. Notably, PIK3CA-Hl047R contained at least two different $CD4^+$ T cell epitopes restricted to different HLA class II alleles.
3. PIK3CA-Hl047R and C-Kit-D816V induced antigen-specific $CD8^+$ T cells as well indicating that they might contain both HLA class I- and class II-restricted epitopes.

4. Immune responses to PIK3CA-Hl047R, C-Kit-D816V, KRAS-G13D, and NRAS-Q61R were observed in more than 10% of the donors.

These findings suggested that frequent driver mutations are not always less immunogenic. Since the identified neoantigens might be not easily lost due to immune escape, they have the potential to be promising off-the-shelf cancer immunotherapy targets in patients with the corresponding mutations.